case report

Multidrug resistant *Acinetobacter* nosocomial meningitis treated successfully with parenteral tigecycline

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Ann Saudi Med 2007; 27(6): 456-458

Infections due to *Acinetobacter* are increasingly identified, most commonly during hospitalization. *Acinetobacter baumannii* is a gram-negative pathogen that targets immunocompromized patients. It is involved less frequently in outpatient health care infections.[1,2]

Catheter-associated blood stream infection (CA-BSI) due to *Acinetobacter* is relatively uncommon, but causes morbidity and extra costs.[3] In several publications, it was found to rank fifth to tenth among pathogens isolated in intensive care units causing CA-BSI[4-7] and is associated with a crude mortality of 43.4%.[4] Lower respiratory tract infections created by nosocomical *Acinetobacter* frequently occur as an outbreak, especially in ventilated patients, causing ventilator-associated pneumonia (VAP).[2] Surgical site infection (SSI) due to *Acinetobacter*, though uncommon, does occur and is increasing in frequency. In a published study, *E. coli* and *Enterobacter* isolates were significantly less commonly reported than *Acinetobacter* isolates ($P<.001$), but *Acinetobacter* comprised only 2.1% of the isolates in 2003[8]. In a retrospective chart review of data from over 16 years, a study from Japan reported that *Acinetobacter* was not found to cause ventriculo-peritoneal shunt infection in adult and pediatric age groups, none of whom had an external CSF drain (cranial or lumbar).[9]

CASE

A 26 year-old male patient was admitted in January 2007 to the Specialty Hospital, Amman, Jordan. He presented with a history of motor vehicle accident in which he sustained multiple injuries to the head, face and extremities. On admission his vitals were: pulse rate 84/minute, blood pressure 115/70 mm Hg, and he was afebrile. He was on a ventilator with multiple trauma to the mouth, right ear, maxillae, mandibles and eyes. His chest examination showed good bilateral air entry, the abdomen was soft, and diagnostic peritoneal lavage was negative. His extremities, neck and back showed skin abrasions. He was unconscious, with reactive pupils–right more than left, and no spontaneous movements. His serum creatinine and electrolytes were normal, and stayed normal all through his illness. SGPT was 100 IU/L, LDH 392 IU/L, and both normalized later. Hemoglobin was 13.2 g/dL on admission, 11.1 g/dL the next day and remained as such until discharge. Several blood cultures as well as urine cultures were sterile. His chest X-ray and cervical spine X-ray showed no abnormality. CT of the brain showed subarachnoid hemorrhage and a basal skull fracture.

On admission he was started on vancomycin and ceftriaxone for a few days. Two days later a percutaneous endoscopic gastrostomy was placed and a lumber external drain was inserted because of evidence of increasing intracranial pressure. Three days later facial reconstructive surgery was done. On the fourth day he became febrile with right lung collapse and an infiltrate. He was started on pipracillin/tazobactam 4.5 g intravenously every 8 hours and amikacin 1 g infusion over one hour once daily. CSF analysis showed WBC 3200/mm^3, polymorphonuclear lymphocytes 27%, lymphocytes 73%, RBC 70/mm^3, glucose 45 mg/dL, protein 60 mg/dL, and culture showed multidrug resistant (MDR) *Acinetobacter*. Subsequent serial CSF cultures 5 and 7 days later grew MDR *Acinetobacter*. The lumbar drain was removed and some clinical improvement was noted. A week later he became confused and febrile with headache; his CSF analysis showed WBC 4300/ mm^3, polymorphs 94%, sugar 55 mg/dL, protein 162 mg/dL, and the culture again showed MDR *Acinetobacter*. He was started on tigecycline monotherapy. While on treatment he had periodic CSF evaluations including gram stains and cultures, each of which were incubated for 5 days in thioglycolate (Table 1). Two days later his

Table 1. CSF evaluations while on tigecycline monotherapy by date.

	29/1	5/2	7/2	15/2	17/2	19/2	21/2	24/2	3/3
WBC /mm^3	3200	NA	NA	4300	280	20	70	30	30
P%	27	NA	NA	94	27	7	8	4	4
L%	73	NA	NA	6	73	90	89	96	96
Glucose mg/dL	45	NA	NA	55	45	60	31	54	52
Protein mg/dL	60	NA	NA	162	186	36	50	62	37
Gram stain	NA	NA	NA	GNB	None	GNB	None	None	None
Culture	NA	Ac	Ac	Ac	NG	NG	CoNS	NG	NG
RBc / mm^3	70	NA	NA	20	20	0	0	0	10

NG = No growth, Ac = MDR Acinetobacter calcoaceticus, P%= Neutrophils, L% = Lymphocytes, MDR = Multidrug resistant, GNB = Gram-negative bacilli, CoNS= Coagulase-negative Staphylococci, NA= Not Available

WBCs became 280/mm^3 with polymorphs 27%, and lymphocytes 73%. The culture was sterile.

Two days later he regained consciousness, with resolution of confusion. The lumber external drain (which stayed for 10 days) was removed. He was continued on tigecycline during his illness and the external drain was removed without the need for a permanent shunt. Coagulase-negative staphylococcus grew later from the cerebrospinal fluid culture; it was interpreted as a contaminant.

DISCUSSION

In the last few years the prevalence of MDR *Acinetobacter* has increased, thus narrowing the therapeutic options. Colomycin has been reintroduced recently as the best option for the treatment of MDR *Acinetobacter* bacteremia. It has also been described in the treatment of ventilator-associated pneumonia as a parenteral agent or in combination with the inhaled form, with good results.[10] Previously, the side effects of colomycin were exaggerated; more recent evaluations indicate its side effects are less serious than once believed. Nephrotoxicity still occurs, but neurotoxicity is exceedingly rare in recent experience.[10,11]

However, newer agents are now available that may add to the treatment armamentarium against MDR *Acinetobacter*. Tigecycline is a relatively new FDA-approved antimicrobial for use in complicated skin and skin structure infections, and complicated intra-abdominal infections, in which polymicrobial infections are likely.[12,13] It also may be used in cases where deep tissue penetration is needed, or where multi-drug resistant pathogens are suspected.[16,17] Tigecycline has good in vitro activity against imipenem-resistant *Acinetobacter*, showing 100% sensitivity.[18,19]

Our patient had a lumbar shunt infection causing meningitis with MDR *Acinetobacter*, which took place during a limited outbreak in the hospital. Due to the difficulty in obtaining colomycin (not registered in Jordan), and the recent availability of tigecycline, the patient was started on the latter antimicrobial.

Tigecycline is the first known glycylcycline. A minocycline derivative, its formula modification enables it to overcome major mechanisms of resistance in the parent tetracycline compounds. i.e., tetracycline-specific efflux pump acquisition and ribosomal protection.[14-17] Its antibacterial spectrum covers aerobic and anaerobic bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate *S. aureus* (VISA), vancomycin-resistant *enterococci* (VRE), and penicillin-resistant *Streptococcus pneumonia* (DRSP),[15,16] as well as extended-spectrum beta-lactamase (ESBL) gram-negative bacteria. Tigecycline is a safe drug for use in treating infections for extended periods of time (up to several months) without experiencing major significant organ toxicity.[20]

Among the non-fermentative gram-negative bacilli such as *Pseudomonas aeruginosa*, tigecycline activity is poor (16% susceptibility), but it is very active against *Acinetobacter* species (96.1% susceptibility at a concentration of ≤4 mg/L) and *Stenotrophomonas maltophilia* (100% susceptibility).[15,16,21] Also it covers "atypical" pathogens. Tigecycline is rapidly distributed and has a large volume of distribution, indicating extensive tissue penetration, and it exhibits time-dependent killing with a post-antibiotic effect (PAE).[17]

In a rabbit model of meningitis, a single dose of tigecycline of 120 mg/kg yielded concentrations in CSF of 11 μg/mL at 3 hours that stayed at a steady level or increased at 6 hours.[15,22] A review of the literature

found no information on tigecycline and CSF levels in humans, in either healthy or inflamed meninges.

Our patient was started on tigecycline 50 mg intravenously twice daily (recommended loading dose, 100 mg). He showed remarkable improvement with subsidence of fever, headache and confusion. On the seventh day the lumbar drain was removed, and he showed continued improvement. Repeat CSF analysis and cultures showed remarkable improvement, though during his treatment course he grew coagulase-negative staphylococci (Table 1). Whether this microbe was a contaminant or a secondary pathogen, it disappeared during treatment with tigecycline. Tigecycline was continued for 21 days, until a week after the last sterile CSF culture. A longer duration of treatment was not deemed necessary, due in part to the rapid and excellent clinical and microbiological response early in the treatment course. The patient was discharged a few days after stopping the treatment. When followed up as an outpatient he was healthy, with no symptoms referred to the previous nosocomial meningitis. In reviewing the literature, I found no other published case for a patient treated with tigecycline for nosocomial meningitis, or external shunt-related meningitis. Controlled trials are needed for this indication, especially since shunt infection is not uncommon.

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